AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Rosuvastatin, Pravastatin, Atorvastatin
ACTIVE INGREDIENT: Rosuvastatin, Pravastatin, Atorvastatin

Study No: D3560L00068
Evaluation of the efficacy and safety of rosuvastatin 5 mg versus pravastatin 40 mg and atorvastatin 10 mg in type IIa and IIb hypercholesterolaemic patients

Developmental phase: Phase IV
Study Completion Date: LSLV = 4 October 2008
Date of Report: 16 September 2009

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Protocol D3560L00068

Evaluation of the efficacy and safety of rosuvastatin 5 mg versus pravastatin 40 mg and atorvastatin 10 mg in type IIa and IIb hypercholesterolaemic patients

Clinical study report summary

Version 2.0 dated 16/09/2009

SUMMARY	
Sponsor	AstraZeneca - 1, place Renault, 92844 Rueil-Malmaison Cedex
Study treatment	Rosuvastatin (Crestor®)
Study title	Evaluation of the efficacy and safety of rosuvastatin 5 mg versus pravastatin 40 mg and atorvastatin 10 mg in type IIa and IIb hypercholesterolaemic patients
Study centres	This French multicentre study was conducted by 190 general practitioners
Study date	First patient included: 12 October 2007 Last patient terminated the study: 04 October 2008
Phase of study	IV
Objectives	
Primary	The primary objective of the study was to compare the variation (as a percentage of baseline values) of LDL-C levels (low density lipoprotein cholesterol) after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg.
Secondary	1. To compare the percentage of patients reaching the LDL-C goal, overall and in relation to the number of risk factors (2 vs. more than 2), according to the French Agency for the Safety of Health Products (AFSSAPS) 2005 guidelines for the management of dyslipidaemic patients, after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg. 2. To compare the variation (as a percentage of baseline values) of total cholesterol, HDL-C (high density lipoprotein cholesterol) and triglycerides after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg. 3. To compare the variation (as a percentage of baseline values) of the Apolipoprotein B/Apolipoprotein A1 ratio after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg. 4. To compare the variation (as a percentage of baseline values) of C-reactive protein (CRP) and phospholipase A2 (PLA2) after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg.

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Study treatment	Rosuvastatin (Crestor®)
	5. To compare the percentage of patients achieving the LDL-C goal according to American guidelines ("National Cholesterol Education Program Adult Treatment Panel III" - NCEP ATP III) for the management of dyslipidaemic patients, after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg. 6. To compare the percentage of patients achieving the LDL-C goal according to European guidelines ("European Atherosclerosis Society" - EAS) for the management of dyslipidaemic patients, after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg. 7. To evaluate the clinical and laboratory safety after 8 weeks of treatment with rosuvastatin 5 mg, pravastatin 40 mg or atorvastatin 10 mg once daily.
Tertiary	To compare the percentage of patients achieving the LDL-C goal according to AFSSAPS 2005, EAS and NCEP ATP III guidelines for the management of hypercholesterolaemic patients in the following 4 subgroups: diabetics (excluding high-risk diabetics), patients with metabolic syndrome, patients with baseline triglycerides (TG) < 2.0 g/l, patients with baseline TG ≥ 2.0 g/l after 8 weeks of treatment with: o rosuvastatin 5 mg versus pravastatin 40 mg or o rosuvastatin 5 mg versus atorvastatin 10 mg.
Methodology	This French multicentre, randomized double-blind study was conducted on three parallel arms (rosuvastatin 5 mg, atorvastatin 10 mg and pravastatin 40 mg), comparing rosuvastatin 5 mg per day to atorvastatin 10 mg per day and rosuvastatin 5 mg per day to pravastatin 40 mg per day in general practice. The 14-week study comprised three visits: a screening visit (week 0, V1), a randomization and treatment allocation visit (week 6, V2) and an evaluation visit (week 14, V3). Patients were randomized at V2 according to a 1:1:1 ratio to one of the three arms and were treated for a period of 8 weeks. Investigation of lipid abnormalities and assay of Apo B, Apo A1, CRP, PLA2 and transaminases were performed at V2 and V3. Creatinine, creatine phosphokinase (CPK) and blood glucose were assayed before visit 2.
Number of patients	It was planned to include 1,150 patients in order to randomize 850 patients. A total of 269 patients per arm were required to detect, with a power to 80%, a difference of 4% for the percentage variation of LDL-C at 8 weeks compared to baseline for two-by-two comparisons of treatment arms, i.e. rosuvastatin 5 mg versus each comparator, atorvastatin 10 mg and pravastatin 40 mg, using a two-tailed test with a limit of significance of 2.5% (Bonferroni correction allowing two comparisons), and a standard deviation of 15%. By estimating that about 5% of randomized patients would drop out of the study, 850 patients had to be randomized. With the hypothesis of 25% of patients not satisfying the randomization criteria, a total of 1,150 patients had to be included. Finally, 668 patients participated in the CAP-Chol study, 558 were included and 317 were randomized (110 patients in the rosuvastatin arm, 104 patients in the atorvastatin arm and 103 patients in the pravastatin arm).
Main inclusion criteria	At visit 1, eligible patients were female or male subjects over the age of 18 with primary hypercholesterolaemia type IIa or IIb diagnosed for at least 3 months, in primary prevention with at least two associated cardiovascular risk factors and: (i) either naive to all lipid-lowering treatment, i.e. not treated by any lipid-lowering drug for at

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Study treatment	Rosuvastatin (Crestor®)
	least 8 weeks and on a diet for at least 3 months; for these patients, LDL-C at the screening visit (V1), based on a recent assessment over the previous 3 months, had to be greater than 1.6 g/l in the presence of 2 other risk factors or greater than 1.3 g/l in the presence of more than 2 other risk factors**,** (ii) or treated with statin (ongoing treatment or treatment stopped during the previous 8 weeks) taking into account the benefit provided to the patient by participation in the study, according to the investigator's judgement. For patients with ongoing treatment, the statin had to be stopped at the screening visit (V1).
Study treatment	
Product	**Rosuvastatin 5 mg**
Route of administration	Oral route
Dosage	Once daily dosage
Treatment regimen	Two capsules (one containing a rosuvastatin 5 mg tablet and the other a placebo capsule)
Reference treatments	
Product	**Pravastatin 20 mg**
Route of administration	Oral route
Dosage	A dose per day
Treatment regimen	Two capsules (each containing a pravastatin 20 mg tablet)
Product	**Atorvastatin 10 mg**
Route of administration	Oral route
Dosage	A dose per day
Treatment regimen	Two capsules (one containing an atorvastatin 10 mg tablet and the other a placebo capsule)
Duration of treatment	8 weeks
Statistical method for the primary endpoint	As the recruitment target was not reached at the date initially planned, and in view of the recruitment difficulties, AstraZeneca decided not to extend the patient recruitment period and to perform only a descriptive analysis of the data, i.e.: o Study populations description and demographic data o Variation of LDL-C between V2 and V3 o Variation of total cholesterol, HDL-C, triglycerides and ApoB/ApoA1 ratio o Variation of CRP and phospholipase A2 o Percentage of patients achieving the NCEP ATP III LDL-C goal o Safety data

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Study treatment	Rosuvastatin (Crestor®)

Population on inclusion

Table R1: Study population

	Rosuvastatin 5 mg	Atorvastatin 10 mg	Pravastatin 40 mg	Total
Population				
Number of patients				
Selected at V1				668
Completed V2				558
Randomized (N)	110	104	103	317
Completed the study (N and%)	102 (92.7%)	97 (93.3%)	91 (88.3%)	290 (91.5%)
Drop-out (N and%)	8 (7.3%)	7 (6.7%)	12 (11.7%)	27 (8.5%)
Number of patients in				
The safety population [a]	110	104	102	316
The analysis population [b]	103 (93.6%)	97 (93.3%)	92 (90.2%)	292 (92.4%)
Demographic characteristics (n = 292)				
Gender (N and%)				
Male	57 (55.34%)	51 (52.58%)	44 (47.83%)	152 (52.05%)
Female	46 (44.66%)	46 (47.42%)	48 (52.17%)	140 (47.95%)
Age (years)				
Mean ± SD	56.71 ± 9.18	57.34 ± 10.74	57.34 ± 9.93	57.12 ± 9.93
Median	55	57	58.5	57
Min; Max	37 ; 78	28 ; 82	26; 81	26 ; 82
Characteristics on inclusion (n = 292)				
BMI (kg/m^2)				
Mean ± SD	28.7 ± 4.34	27.24 ± 4.51	27.73 ± 4.63	27.91 ± 4.52
Median	28.35	27.05	26.73	27.51
Min; Max	19.10 ; 44.06	17.96 ; 43.11	18.72 ; 42.98	17.96 ; 44.06
Treatment of hyperlipidaemia [C] (N and%)				
Treatment-naive patient s	67 (65.69%)	61 (62.89%)	63 (68.48%)	191 (65.64%)
Patients treated with statin	35 (34.31%)	36 (37.11%)	29 (31.52%)	100 (34.36%)
Number of risk factors (N and%)				
Patients with 0-1 RF	2 (1.94%)	2 (2.06%)	2 (2.17%)	6 (2.05%)
Patients with 2-3 RFs	95 (92.23%)	84 (86.60%)	84 (91.30%)	263 (90.07%)
Patients with more than 3 RFs	6 (5.83%)	11 (11.34%)	6 (6.52%)	23 (7.88%)

[a]: Numbers of randomized patients who took at least one dose of treatment

[b] : Number of randomized patients who took at least one dose of treatment, in whom a lipid value at randomization (V2) and a lipid value obtained subsequently during treatment (V3) were available. The primary endpoint was evaluated on this population of 292 patients.

[c] :missing data = 1

N = Number; SD = standard deviation; CI = confidence interval; BMI = body mass index; RF = risk factor;

The proportion of patients who dropped out of the study was higher in the pravastatin arm. Patients were predominantly males, except in the pravastatin arm. The mean age was 57.1 ± 9.9 years and the mean BMI was 27.9 ± 4.5 kg/m^2. A greater number of patients presented more than 3 RFs in the atorvastatin arm.

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Study treatment	Rosuvastatin (Crestor®)

Efficacy results

Table R2: Results

Objectives	Results
Main To compare the variation (as a percentage of baseline values) of LDL-C after 8 weeks of treatment with: o rosuvastatin 5 mg o pravastatin 40 mg o atorvastatin 10 mg.	A mean relative decrease of LDL-C of -35.9 ± 16.3% was observed in the analysis population (N = 292) after 8 weeks of treatment. This variation was respectively: o -37.6 ± 18.0% for patients treated with rosuvastatin 5 mg o -30.3 ± 15.4% for patients treated with pravastatin 40 mg o -39.4 ± 13.8% for patients treated with atorvastatin 10 mg
Secondary To compare after 8 weeks of treatments in the 3 arms: rosuvastatin 5 mg, pravastatin 40 mg, and atorvastatin 10 mg: o The variation (as a % of baseline values) of total cholesterol, HDL-C and triglycerides o The variation (as a % of baseline values) of the ApoB/ApoA1 ratio o The variation (as a % of baseline values) of CRP and PLA2	See table below
To determine the percentage of patients achieving the LDL-C goal according to American guidelines (NCEP ATP III) for the management of dyslipidaemic patients.	The percentage of patients achieving the NCEP-ATP III LDL-C goal was 35.1% (N = 102) with: o 80.4% (N = 82) of patients presenting 2 or more risk factors o 19.6% (N = 20) of diabetic patients.

Analysis population	Treatment arms: Rosuvastatin 5 mg N=103	Atorvastatin 10 mg N=97	Pravastatin 40 mg N=92	Total N=292
	(Mean % ± SD)			
Total cholesterol	-25.2 ± 14.0	-28.6 ± 11.0	-20.4 ± 11.7	-24.8 ± 12.8
HDL-C	11.3 ± 20.6	4.4 ± 14.3	7.9 ± 19.2	7.9 ± 18.4
Triglycerides	-8.7 ± 37.0	-19.2 ± 25.0	-6.1 ± 31.6	-11.4 ± 32.1
ApoB/ApoA1	-31.9 ± 17.0	-30.9 ± 14.7	-26.0 ± 13.5	-29.7 ± 15.4
CRP	15.2 ± 104.9	37.3 ± 187.4	33.1 ± 184.2	28.2 ± 161.6
PLA2	2.9 ± 24.2	5.6 ± 46.4	13.0 ± 73.6	7.0 ± 51.5

Safety results

The total number of AEs during the study was 46 events for 23 patients (7.3% of patients of the safety population).

The organ systems most commonly affected were:

- musculoskeletal and connective tissue disorders (3.2% of patients)

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- o infections and infestations (1.6% of patients)
- o gastrointestinal disorders (1.3% of patients).

The most commonly observed AEs were muscle contractures (3 AEs) and myalgia (3 AEs). The majority of AEs was mild (19.6%) or moderate (73.9%). Only 3 AEs (with atorvastatin) were severe.

Among these 46 AEs, 22 (8 patients) were considered by the investigator to be treatment-related. The treatment-related AEs most commonly observed were muscle disorders, including muscle contractures (3 AEs), myalgia (3 AEs) and nausea (2 AEs).

No death was reported during the study. Seven events were declared to be serious (SAE) by the investigators: two SAEs (2 patients) before randomization and five SAEs (5 patients) after randomization. Only one SAE was considered to be related to the study treatment (in the atorvastatin 10 mg arm).

Table R3: Patients experiencing at least one AE and total number of AEs and per treatment arm during treatment period

Treatment arm	Rosuvastatin 5 mg N=110	Atorvastatin 10 mg N=104	Pravastatin 40 mg N=102	Total N=316
Number of patients experiencing at least one AE*				
AE	5 (4.55%)	9 (8.65%)	9 (8.82%)	23 (7.28%)
Treatment-related AE	4 (3.64%)	2 (1.92%)	2 (1.96%)	8 (2.53%)
SAE	0 (0.0%)	4 (3.85%)	1 (0.98%)	5 (1.58%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other SAE	0 (0.0%)	4 (3.85%)	1 (0.98%)	5 (1.58%)
Treatment-related SAE	0 (0.0%)	1 (0.96%)	0 (0.0%)	1 (0.32%)
AE leading to permanent discontinuation of treatment	4 (3.64%)	3 (2.88%)	2 (1.96%)	9 (2.85%)

Total number of AEs**	**N=11**	**N=11**	**N=24**	**N=46**
Treatment-related AE	10 (90.91%)	2 (18.18%)	10 (41.67%)	22 (47.83%)
SAE	0 (0.0%)	4 (36.36%)	1 (4.17%)	5 (10.87%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other SAE	0 (0.0%)	4 (36.36%)	1 (4.17%)	5 (10.87%)
Treatment-related SAE	0 (0.0%)	1 (9.09%)	0 (0.0%)	1 (2.17%)
AE leading to permanent discontinuation of treatment	10 (90.91%)	3 (27.27%)	7 (29.17%)	20 (43.48%)

* : Percentages were calculated with respect to the number of patients in the safety population (in each arm, respectively)

** : Percentages were calculated with respect to the total number of AEs (in each arm, respectively)